REMARKS

Applicant respectfully requests reconsideration. Claims 1-27, 32, 53, 54, 76, 78, 158, 175, 195, 198 and 199 were previously pending in this application. Claims 1-9, 11, 12, 27, 32, 53, 54, 76, 158, 175 and 195 are withdrawn from consideration. Claims 10, 78, 198 and 199 have been amended. Claim 10 has been amended to clarify the claim language. Claim 78 has been amended to add the recitation "wherein the polypeptide does not contain Cys residues". Support for this amendment is found on page 50, lines 3-4. Claims 198 and 199 have been amended to correct a typographical error. As a result, claims 10, 13-26, 78, 198 and 199 are pending for examination with claims 10, 78 and 198 being independent claims. No new matter has been added.

Withdrawal of Rejections

Applicant thanks the Examiner for the withdrawal of the rejection of claim 10 under 35 U.S.C. § 112, second paragraph, as being indefinite. The rejection of claims 10, 13 and 14 and claims 10 and 13-18 under 35 U.S.C. § 102(b) as being anticipated by Bittle *et al.* and Soker *et al.* respectively, has been withdrawn. The rejection of claims 10 and 13-26 under 35 U.S.C. § 102(e) as being anticipated by Wescott *et al.* has also been withdrawn.

Objections to the Specification

The Examiner objected to the specification for an informality in the recitation of SEQ ID NO:377. Applicant has amended the specification to correct a typographical error as suggested by the examiner. No new matter has been added.

Accordingly, withdrawal of this objection is respectfully requested.

Claim Objections

The Examiner has objected to claims 198 and 199 for a typographical error in the amino acid sequence identifiers. Applicant has amended claims 198 and 199 to correct this typographical error as suggested by the Examiner. No new matter has been added.

Accordingly, withdrawal of the objection to claims 198 and 199 is respectfully requested.

Double Patenting Rejection

The Examiner rejected claim 78, 198 and 199 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 1 and 11-20 of U.S. Patent No. 7,211,240.

Applicant respectfully disagrees. Nonetheless, Applicant notes that it may remove the rejection with a terminal disclaimer when the claims are otherwise indicated as allowable. *See* MPEP § 804.02.

Rejections under 35 U.S.C. §112

The Examiner rejected claims 10, 13-26 and 78 under 35 U.S.C. §112, first paragraph as failing to comply with the written description requirement. According to the Examiner, the claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor had possession of the claimed invention.

Applicant respectfully disagrees. An actual reduction to practice and working examples are not required to demonstrate that Applicant had possession of the invention. According to MPEP § 2163.02 "An objective standard for determining compliance with the written description requirement is, 'does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed.'....to satisfy the written description requirement, an applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention, and that the invention, in that context, is whatever is now claimed." An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. *Lockwood v. American Airlines, Inc.,* 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997). To show that the claims are adequately described in the specification, Applicant has identified the written support in the specification for each element recited in claims 10, 13-26 and 78.

Claim 10:

An isolated polypeptide having the ability to bind to kinase domain region (KDR) or vascular endothelial growth factor/kinase domain region (VEGF/KDR) complex comprising an amino acid sequence of one of the following

Support is found on page 4, lines 15-17 and page 46, lines 11-12:

"A group of polypeptides has been discovered that bind to KDR or VEGF/KDR complex (referred to herein as "KDR binding polypeptides" or"KDR binding moieties" and homologues thereof)."

"The present invention provides novel binding moieties that bind KDR or a complex of VEGF and KDR."

Consensus Sequence 13: Z_1-X_1-X_2-X_3-X_4-X_5-Z_2

Support is found on page 16, line 21:

"Consensus Sequence 13: Z_1-X_1-X_2-X_3-X_4-X_5-Z_2 (Lin20)"

wherein, Z_1 is a polypeptide of at least one amino acid or is absent;

X_1 is Ala, Asp, Gln or Glu;

X_2 is Ala, Asp, Gln, Glu, Pro;

X_3 is Ala, Leu, Lys, Phe, Pro, Trp or Tyr;

X_4 is Asp, Leu, Ser, Trp, Tyr or Val;

X_5 is Ala, Arg, Asp, Glu, Gly, Leu, Trp or Tyr; and

Z_2 is a polypeptide of at least one amino acid or is absent;

Support is found on page 16, lines 22-28:

"Z_1 is a polypeptide of at least one amino acid or is absent;

X_1 is Ala, Asp, Gln or Glu (preferably Gln or Glu);

X_2 is Ala, Asp, Gln, Glu, Pro (preferably Asp, Glu or Gln);

X_3 is Ala, Leu, Lys, Phe, Pro, Trp or Tyr (preferably Trp, Tyr, Phe or Leu);

X_4 is Asp, Leu, Ser, Trp, Tyr or Val (preferably Tyr, Trp, Leu or Val);

X_5 is Ala, Arg, Asp, Glu, Gly, Leu, Trp or Tyr (preferably Trp, Tyr or Leu); and

Z_2 is a polypeptide of at least one amino acid or is absent"

Further, sequences identified as SEQ ID NOs:137, 140, 142, 147, 149, 156, 162, 164, 169, 171, 185, 304, 306, 308, 331, 343, 344, 353 and 356, fall within the scope of this consensus

sequence (see pages 136-137, Table 3 and pages 145-146, Table 8) and all were demonstrated to bind to KDR (see page 133, lines 15-19). SEQ ID NOs:304, 306 and 308 were shown to bind KDR and/or VEGF/KDR (see Table 8, pages 146-147). SEQ ID NO:356 is disclosed as a biotinylated peptide and was demonstrated to bind well to KDR-expressing cells (see page 148, lines 13-14) and exhibited the best K_D for binding to KDR expressing cells when tested as a biotinylated tetrameric complex containing a JJ spacer (see page 151, lines 6-12, Figure 2 and Figure 5).

Consensus Sequence 14: X_1–X_2–X_3–Tyr–Trp–Glu–X_7–X_8–X_9–Leu (SEQ ID NO:7)

Support is found on page 17, lines 1-2:

"Consensus Sequence 14: X_1–X_2–X_3–Tyr–Trp–Glu–X_7–X_8–X_9–Leu (SEQ ID NO:7)"

wherein, the sequence can optionally have a N-terminal polypeptide, C-terminal polypeptide, or a polypeptide at both termini of at least one amino acid

Support is found on page 17, lines 3-4:

"wherein, the sequence can optionally have a N-terminal polypeptide, C-terminal polypeptide, or a polypeptide at both termini of at least one amino acid"

wherein, X_1 is Asp, Gly or Ser;

X_2 is Ile, Phe or Tyr;

X_3 is Ala, Ser or Val;

X_7 is Gln, Glu, Ile or Val;

X_8 is Ala, Ile or Val and;

X_9 is Ala, Glu, Val or Thr,

Support is found on page 17, lines 5-11:

"wherein, X_1 is Asp, Gly or Ser (preferably Gly);

X_2 is Ile, Phe or Tyr;

X_3 is Ala, Ser or Val;

X_7 is Gln, Glu, Ile or Val;

X_8 is Ala, Ile or Val (preferably Ile or Val);

X_9 is Ala, Glu, Val or Thr

Further, sequences identified as SEQ ID NOs:138, 141, 146, 170, 175, 305 and 307 fall within the scope of this consensus sequence and were demonstrated to bind to KDR and/or VEGF/KDR (see pages 136-137, Table 3 and pages 146-147, Table 8). For example, SEQ ID NOs:305 and 307 were shown to bind KDR and/or VEGF/KDR (see Table 8, pages 146-147).

wherein the polypeptide does not contain Cys residues

Support is found on page 50, lines 3-4:

"The amino acids at each position in the template were varied to permit any amino acid except cysteine (Cys)."

and wherein the polypeptide is conjugated to one or more detectable labels or therapeutic agents.

Support is found on page 26, lines 27-28:

"the polypeptide can be conjugated to a detectable label or a therapeutic agent"

Claim 13:

The polypeptide of claim 10, wherein the polypeptide further comprises N-terminal and/or C-terminal flanking peptides of one or more amino acids.

Support is found on page 26, lines 21-22:

"the amino acid sequence further comprises N-terminal and/or C-terminal flanking peptides of one or more amino acids"

Further, sequences identified as SEQ ID NOs:137, 138, 140-142, 146, 147, 149, 156, 162, 164, 169-171, 175, 185, 304-308, 331, 343, 344, 353 and 356 are sequences that comprise the claimed consensus sequences and also include various N-terminal and/or C-terminal flanking peptides of one or more amino acids. As stated above, these peptides have been demonstrated to bind KDR and/or VEGF/KDR as claimed.

Claim 14:

The polypeptide of claim 10, wherein the polypeptide comprises a modification selected from the group consisting of: an amino acid substitution, an amide bond substitution, a D-amino acid substitution, a glycosylated amino acid, a disulfide bond, a disulfide mimetic substitution, an amino acid translocation, a retroinverso peptide, a peptoid, a retro-inverso peptoid, and a synthetic peptide.

Support is found on page 26, lines 22-26:

> "the amino acid sequence comprises a modification selected from the group consisting of: an amino acid substitution, an amide bond substitution, a D-amino acid substitution, a glycosylated amino acid, a disulfide bond, a disulfide mimetic substitution, an amino acid translocation, a retroinverso peptide, a peptoid, a retro-inverso peptoid, and a synthetic peptide."

Claim 15:

The polypeptide of claim 10, wherein the polypeptide further comprises a linker or spacer between the polypeptide and the detectable label or the therapeutic agent.

Support is found on page 26, line 28 to page 27, line 1:

> "further comprising a linker or spacer between the polypeptide and the detectable label or the therapeutic agent."

Further, sequence SEQ ID NOs:343, 344, 353 and 356 are disclosed in the specification as comprising a JJ spacer (see page 150, Table 10) and have been demonstrated to bind KDR and/or VEGF/KDR.

Claim 16:

The polypeptide of Claim 15, wherein the detectable label or the therapeutic agent is selected from the group consisting of: an enzyme, a fluorescent compound, a liposome, an optical dye, one or more paramagnetic metal ions or a superparamagnetic particle, an ultrasound contrast agent and one or more radionuclides.

Support is found on page 27, lines 1-4 and lines 14-16:

"the detectable label or the therapeutic agent is selected from the group consisting of: an enzyme, a fluorescent compound, a liposome, an optical dye, a paramagnetic metal ions or a superparamagnetic particle, an ultrasound contrast agent and a radionuclide."

"the detectable label can comprise one or more paragmagnetic metal ions or a superparamagnetic particle or one or more chelators."

Claim 17:

The polypeptide of Claim 16, wherein the therapeutic agent or detectable label comprises one or more radionuclides.

Support is found on page 28, line 1:

"comprise at least one radionuclide"

Claim 18:

The polypeptide of Claim 17, wherein the radionuclide is selected from the group consisting of: ^{18}F, ^{124}I, ^{125}I, ^{131}I, ^{123}I, ^{77}Br, ^{76}Br, ^{99m}Tc, ^{51}Cr, ^{67}Ga, ^{68}Ga, ^{47}Sc, ^{51}Cr, ^{167}Tm, ^{141}Ce, ^{111}In, ^{168}Yb, ^{175}Yb, ^{140}La, ^{90}Y, ^{88}Y, ^{153}Sm, ^{166}Ho, ^{165}Dy, ^{166}Dy, ^{62}Cu, ^{64}Cu, ^{67}Cu, ^{97}Ru, ^{103}Ru, ^{186}Re, ^{188}Re, ^{203}Pb, ^{211}Bi, ^{212}Bi, ^{213}Bi, ^{214}Bi, ^{105}Rh, ^{109}Pd, ^{117m}Sn, ^{149}Pm, ^{161}Tb, ^{177}Lu, ^{198}Au *and* ^{199}Au.

Support is found on page 27, lines 6-9:

"comprises a radionuclide including, for example, ^{18}F, ^{124}I, ^{125}I, ^{131}I, ^{123}I, ^{77}Br, ^{76}Br, ^{99m}Tc, ^{51}Cr, ^{67}Ga, ^{68}Ga, ^{47}Sc, ^{51}Cr, ^{167}Tm, ^{141}Ce, ^{111}In, ^{168}Yb, ^{175}Yb, ^{140}La, ^{90}Y, ^{88}Y, ^{153}Sm, ^{166}Ho, ^{165}Dy, ^{166}Dy, ^{62}Cu, ^{64}Cu, ^{67}Cu, ^{97}Ru, ^{103}Ru, ^{186}Re, ^{188}Re, ^{203}Pb, ^{211}Bi, ^{212}Bi, ^{213}Bi, ^{214}Bi, ^{105}Rh, ^{109}Pd, ^{117m}Sn, ^{149}Pm, ^{161}Tb, ^{177}Lu, ^{198}Au or ^{199}Au."

Claim 19:

The polypeptide of Claim 18, wherein the therapeutic agent or detectable label further comprises a chelator.

Support is found on page 27, lines 9-10:

"the therapeutic agent or detectable label further comprises a chelator"

Claim 20:

The polypeptide of Claim 19, wherein the chelator comprises a compound selected from the group consisting of: formula 20, 21, 22, 23a, 23b, 24a, 24b, and 25.

Support is found on page 27, lines 10-11:

> "a chelator, such as, for example, a compound selected from the group consisting of: formula 20, 21, 22, 23a, 23b, 24a, 24b, and 25."

Claim 21:

The polypeptide of Claim 19, wherein the radionuclide is ^{99m}Tc or ^{111}In.

Support is found on page 28, lines 5-6:

> "In one embodiment, the radionuclide is selected from the group consisting of ^{99m}Tc and ^{111}In."

Claim 22:

The polypeptide of Claim 19, wherein the radionuclide is selected from the group consisting of: ^{177}Lu, ^{90}Y, ^{153}Sm and ^{166}Ho.

Support is found on page 28, lines 17-18:

> "the radionuclide is selected from the group consisting of: ^{177}Lu, ^{90}Y, ^{153}Sm and ^{166}Ho."

Claim 23:

The polypeptide of Claim 16, wherein the detectable label comprises an ultrasound contrast agent.

Support is found on page 27, line 12:

> "the detectable label comprises an ultrasound contrast agent"

Claim 24:

The polypeptide of Claim 23, wherein the ultrasound contrast agent is a phospholipid stabilized microbubble or an ultrasound contrast agent comprising a gas.

Support is found on page 27, lines 13-14:

"an ultrasound contrast agent that can comprise, for example, a phospholipid stabilized microbubble or a microballoon comprising a gas"

Claim 25:

The polypeptide of Claim 24, wherein the ultrasound contrast agent comprises a fluorinated gas.

Support is found on page 27, line 23:

"further comprise a fluorinated gas"

Claim 26:

The polypeptide of Claim 16, wherein the detectable label comprises one or more paramagnetic metal ions and one or more chelators.

Support is found on page 27, lines 14-16:

"the detectable label can comprise one or more paramagnetic metal ions or a superparamagnetic particle and one or more chelators."

Claim 78:

A multimeric polypeptide construct having the ability to bind to KDR or VEGF/KDR complex comprising at least one amino acid sequence of one of the following:

Support is found on page 4, lines 15-17 and page 5, lines 9-11:

"A group of polypeptides has been discovered that bind to KDR or VEGF/KDR complex (referred to herein as "KDR binding polypeptides" or "KDR binding moieties" and homologues thereof)."

"This invention pertains to KDR and VEGF/KDR binding polypeptides, and includes use of a single binding polypeptide as a monomer or in a multimeric or polymeric construct"

Consensus Sequence 13: Z_1-X_1-X_2-X_3-X_4-X_5-Z_2

Support is found on page 16, line 21:

"Consensus Sequence 13: Z_1-X_1-X_2-X_3-X_4-X_5-Z_2 (Lin20)"

wherein, Z_1 is a polypeptide of at least one amino acid or is absent;

X_1 is Ala, Asp, Gln or Glu;

X_2 is Ala, Asp, Gln, Glu, Pro;

X_3 is Ala, Leu, Lys, Phe, Pro, Trp or Tyr;

X_4 is Asp, Leu, Ser, Trp, Tyr or Val;

X_5 is Ala, Arg, Asp, Glu, Gly, Leu, Trp or Tyr; and

Z_2 is a polypeptide of at least one amino acid or is absent;

Support is found on page 16, lines 22-28:

"Z_1 is a polypeptide of at least one amino acid or is absent;

X_1 is Ala, Asp, Gln or Glu (preferably Gln or Glu);

X_2 is Ala, Asp, Gln, Glu, Pro (preferably Asp, Glu or Gln);

X_3 is Ala, Leu, Lys, Phe, Pro, Trp or Tyr (preferably Trp, Tyr, Phe or Leu);

X_4 is Asp, Leu, Ser, Trp, Tyr or Val (preferably Tyr, Trp, Leu or Val);

X_5 is Ala, Arg, Asp, Glu, Gly, Leu, Trp or Tyr (preferably Trp, Tyr or Leu); and

Z_2 is a polypeptide of at least one amino acid or is absent"

Consensus Sequence 14: X_1–X_2–X_3–Tyr–Trp–Glu–X_7–X_8–X_9–Leu (SEQ ID NO:7)

Support is found on page 17, lines 1-2:

"Consensus Sequence 14: X_1–X_2–X_3–Tyr–Trp–Glu–X_7–X_8–X_9–Leu (SEQ ID NO:7)"

wherein, the sequence can optionally have a N-terminal polypeptide, C-terminal polypeptide, or a polypeptide at both termini of at least one amino acid

Support is found on page 17, lines 3-4:

"wherein, the sequence can optionally have a N-terminal polypeptide, C-terminal polypeptide, or a polypeptide at both termini of at least one amino acid"

wherein, X_1 is Asp, Gly or Ser;

X_2 is Ile, Phe or Tyr;

X_3 is Ala, Ser or Val;

X_7 is Gln, Glu, Ile or Val;

X_8 is Ala, Ile or Val and;

X_9 is Ala, Glu, Val or Thr,

Support is found on page 17, lines 5-11:

"wherein, X_1 is Asp, Gly or Ser (preferably Gly);

X_2 is Ile, Phe or Tyr;

X_3 is Ala, Ser or Val;

X_7 is Gln, Glu, Ile or Val;

X_8 is Ala, Ile or Val (preferably Ile or Val);

X_9 is Ala, Glu, Val or Thr

wherein the polypeptide does not contain Cys residues.

Support is found on page 50, lines 3-4:

"The amino acids at each position in the template were varied to permit any amino acid except cysteine (Cys)."

Therefore, the claims are fully supported by the specification.

The Examiner has cited the MPEP § 2163 as stating that "for a generic claim the genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus" (see Office Action, page 6). Applicant has disclosed the sequences for SEQ ID NOs:137, 138, 140-142, 146, 147, 149, 156, 162, 164, 169-171, 175, 185, 304-308, 331, 343, 344 and 353 (a total of 25 sequences) which fall within the scope of the consensus sequences recited in independent claims 10 and 78. These peptides were demonstrated to bind to KDR and/or VEGF/KDR (see page 145-147, Table 8; pages 149-150, Table 10). As stated above, these 25 sequences include various flanking sequences (represented by Z_1 and Z_2 in the claimed consensus sequence) and remain capable of binding KDR and/or VEGF/KDR. Sequences SEQ ID NOs:137, 138, 140-142, 146, 147, 149, 156, 162, 164, 169-171, 175 and 185 are further disclosed as fusion proteins. Such fusion proteins were shown to be capable of binding KDR and/or VEGF/KDR. Further, SEQ ID NO:356 is disclosed as a biotinylated peptide and was demonstrated to bind well to

KDR-expressing cells (see page 148, lines 13-14) and exhibited the best K_D for binding to KDR expressing cells when tested as a biotinylated tetrameric complex containing a JJ spacer (see page 151, lines 6-12, Figure 2 and Figure 5).

Applicant has therefore demonstrated possession of at least 25 specific amino acid sequences that fall within the scope of the claims and have demonstrated the function of such claimed peptides, i.e. binding to KDR and/or VEGF/KDR. Applicant submits that 25 peptides each having variations as encompassed by the claims is a representative number of species to demonstrate possession of the genus.

Accordingly, withdrawal of the rejection of claims 10, 13-26 and 78 under 35 U.S.C. §112, first paragraph, is respectfully requested.

CONCLUSION

Applicant respectfully requests reconsideration. The Examiner is requested to call the undersigned at the telephone number listed below if this communication does not place the case in condition for allowance.

A check in the amount of $1,860.00 is enclosed to cover the three month extension of time and Request for Continued Examination fee. If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. If there is a fee occasioned by this response, including an extension fee, that is not covered by an enclosed check, please charge any deficiency to Deposit Account No. 23/2825, under Docket No. D0617.70012US00.

Dated: January 28, 2008

Respectfully submitted,

By 

Marie A. Aucoin, Ph.D.
Registration No.: 59,414
WOLF, GREENFIELD & SACKS, P.C.
Federal Reserve Plaza
600 Atlantic Avenue
Boston, Massachusetts 02210-2206
(617) 646-8000